living being not infected with Chlamydia pneumoniae."

It is submitted that this rejection does not take into account the fact that macrolide antibiotics have been claimed to have anti-inflammatory activities distinct from their antibiotic function that may make them useful for treatment of non-C. pneumoniae infected individuals (Pharmacol Res. 2001 Dec;44(6):451-4). The authors of the above referenced paper are quoted in saying "Macrolide antibiotics play a significant role in clinical practice due not only to their antibacterial activity, but also to their accompanying anti-inflammatory effect that is independent of their antibiotic action."

In 144 published papers related to the issue of non-antibiotic activity of macrolide and other antibiotics, none suggested their use in patients with Alzheimer's disease, and thus, the use of these antibiotic's anti-inflammatory activity may be effective without consideration of whether the patient has confirmed Chlamydia pneumoniae infection. Thus, Applicants respectfully request that this rejection be withdrawn.

Claims 8-17 were rejected under 35 U.S.C. §103(a) as being unpatentable over Shor et al in combination with Koskiniemi et al. As stated in the rejection, "Shor et al disclose the use of a macrolide alone or in combination with an anti-inflammatory agent for the treatment of Chlamydia pneumoniae infection but do not disclose the treatment of said infection in (the) central nervous system. However, since Koskiniemi et al disclose Chlamydia pneumoniae infections associated with CNS, a person having ordinary skill in the art at the time the instant invention was made would have been motivated to treat any disease which involves infection by C. pneumoniae of CNS with a macrolide or a macrolide in combination with an anti-inflammatory agent because the results obtained from such treatment would have been expected."

Applicants respectfully transverse this rejection and submit that it is not true that one knowledgeable in the art would not immediately recognize that an effective treatment for meningitis would necessarily work for treating infection in cells such as glial cells and astrocytes shown to be infected in our invention. In fact, treatment of a chronic infection by Chlamydia pneumoniae of glial cells and astrocytes compared to acute infection of the CNS are as distinct as endothelial cell infection (Shor et al) compared to an acute infection of the lungs (original observation).

Data demonstrating at least stabilization of disease (as shown in our invention) would be required before one knowledgeable in the art would chose a particular antibiotic. Data demonstrating similar efficacy to the present invention is the basis for use of presently available therapeutics for Alzheimer's, i.e., transient improvement or stabilization of disease.

Furthermore, in one example Applicants provided, although preliminary, explicitly demonstrate that their treatment can result in an improvement in MMSE scores going from less than 10 before antibiotic treatment to a score of 16 after 9 month treatment with azithromycin 250 mg daily. This individual also had an improvement in their clock drawing skills.

A person knowledgeable in the art would recognize these results as suggestive that antibiotic therapy may be useful in treating Alzheimer's Disease. However, these results could not have been predicted by the same antibiotics efficacy in meningitis, particularly when using the information provided by Koskiniemi et al.

Koskiniemi et al. did not define the cell type being infected, nor did they confirm that the meningitis was actually due to infection by C. pneumoniae. Furthermore, assuming that the limited responses observed in their paper were due to reduction or elimination of a C. pneumoniae infection, it would not be convincing that such a treatment would be effective for reducing or eliminating an

infection in glial cells or astrocytes.

Applicants also submit the Declaration of Dr. Steve Feinstein in support of the patentability of the above invention. Dr. Feinstein indicates that first and foremost, in his expert opinion, the observations reported within the patent application, when confirmed, would represent a complete shift in the focus of therapy for patients with Alzheimer's disease, from barely treating the symptoms to aggressively attempting to prevent its onset.

Dr. Feinstein states further that there is no known cause of sporadic Alzheimer's disease and this body of work represents the first completely new research approach in many years.

Dr. Feinstein states that the work of Koskiniemi et al. is a poor example of effective treatment for CNS infection by Chlamydia pneumoniae. The authors never proved that there was an active Chlamydia pneumoniae infection in the CNS in any of the meningitis patients described. This is in direct contrast to the large body of work provided in the Balin application that proved the presence of Chlamydia pneumoniae in 17 of 19 patients who suffered from Alzheimer's disease.

Dr. Feinstein further concludes that Koskiniemi et al is deficient as a reference because they do not define the cell type infected and thus, do not teach sufficiently to use their observations as a model to treat other patients with Chlamydia pneumoniae infection related to chronic neurologic disease.

Dr. Feinstein points out that the Koskiniemi reference does not show whether the antibiotic treatment described resulted in suppression of said infection versus clearance of bacteria. Given these flaws, as well as the fact that as a clinician he would be making a therapeutic decision for chronic infections rather than an acute infection described by Koskiniemi et al, he would not be comfortable using it as a model for treating Chlamydia pneumoniae infections related to Alzheimer's

disease.

In fact, Dr. Feinstein does not think Koskiniemi et al. even teaches effectively the appropriate treatment of Chlamydia pneumoniae associate meningitis.

Accordingly, in view of the above remarks, Applicants respectfully request favorable reconsideration of this application.

Applicants would also be willing to hold a personal interview with the Examiner if it is felt that this would expedite allowance of this case.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

April 24 2002

By

Robert S. Silver
Seven Penn Center
1635 Market Street - 12th Floor
Philadelphia, PA 19103-2212
(215) 567-2-2010
Attorneys for Applicants

CERTIFICATE OF MAILING

I hereby certify that the foregoing AMENDMENT, Transmittal Sheet, in duplicate, along with a PETITION FOR EXTENSION OF TIME in duplicate, and Declaration of Dr. Steve Feinstein, re Application Serial No. 09/227,749 are being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on this 24th day of April, 2002.

Robert S. Silver